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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/215,163	12/18/1998	JEFFREY R. STINSON	04995.0032-0	7721

21874 7590 05/17/2004

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EXAMINER	
ZEMAN, ROBERT A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/215,163	STINSON ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 March 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *see attached*.

3. ☐ Applicant's reply has overcome the following rejection(s): see attached.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1, 2, 14, 17-20, 23, 29 and 32-43*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

ADVISORY ACTION

The amendment filed 3-24-2004 under 37 CFR 1.116 in reply to the final rejection has been considered but is not deemed to place the application in condition for allowance and will not be entered because:

The proposed amendment raises new issues that would require further consideration and/or search. For instance, the proposed amendment to claim 1 (in addition to requiring a new search) would minimally raise new issues under 35 U.S.C. 112, second paragraph.

It should be noted that Applicant's arguments are predicated on amendments not made of record and hence are deemed non-persuasive. All arguments not relying on said amendment are addressed below.

Claim Rejections Maintained

Double Patenting

The rejection of claim 41 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,747,272 is maintained for reasons of record. Applicant has indicated that they address said rejection once there is indication of allowable subject matter.

Claims 1-2, 14, 17-20, 23, 29 and 32-43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,747,272 in view of Carter et al. (WO 94/04679) is maintained for reasons set forth in the

rejection of claims 1-2, 13-20, 23, 29 and 32-41 in the previous Office action. Applicant has addressed this rejection in his response.

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1, 2, 14, 17-20, 29, 32-40 and 43-44 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for humanized monoclonal antibodies based on monoclonal antibodies 13C4 or 11E10 (**defined regions**), does not reasonably provide enablement for humanized antibodies "containing at least part of a murine immunoglobulin variable region as shown in Figure 3 (SEQ ID NO:21 or Figure 6 (SEQ ID NO:42), wherein the antibody specifically reacts with Stx1 or Stx2 antigen or portions of SEQ ID NO:42 or SEQ ID NO:44 is maintained for the reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims.

Since the amendment was not entered the instant claims merely require that the murine immunoglobulin variable region have **one amino acid** in common with the variable regions depicted in Figures 3 or Figure 6 or SEQ ID NO:42 or SEQ ID NO:44 (i.e. "at least part of..."). In response to applicant's argument that the specification is enabling since the instant claims recite functional language, it is noted that the features upon which applicant relies (i.e., the claimed antibody must bind antigen) are not recited in the rejected claim(s). The instant claims

merely require that the claimed antibody "specifically reacts with Stx1 or Stx2 antigen. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Finally, as outlined previously, the specification outlines the materials and methods needed to make humanized antibodies utilizing the 13C4 or 11E10 monoclonal antibodies. However, the specification is silent on the sequences of the murine variable region required to confer function on the chimeric antibody the location (or sequence) of the immunogenic epitopes. Given the lack of guidance contained in the specification and the unpredictability in determining acceptable sequence variations, one of skill in the art could not make the broadly claimed invention without undue experimentation.

The rejection of claims 23, 29 and 39-40 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical compositions comprising humanized monoclonal antibodies based on monoclonal antibodies 13C4 or 11E10 (**defined sequences**), does not reasonably provide enablement for pharmaceutical compositions comprising humanized antibodies "containing at least part of a murine immunoglobulin variable region as shown in Figure 3 (SEQ ID NO:21 or Figure 6 (SEQ ID NO:42), wherein the antibody specifically reacts with Stx1 or Stx2 antigen or portions of SEQ ID NO:42 or SEQ ID NO:44 is maintained for reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims. Since the amendment has not been entered the instant claims still

read on pharmaceutical compositions. Therefore, as outlined previously, the specification is silent on how the claimed compositions would be used and equally silent on the efficacy of a given composition. Since no evidence has been provided that illustrates or even suggests that the claimed pharmaceutical compositions are capable of eliciting a beneficial therapeutic response, one of skill in the art would not be able to make and use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 20 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of term "variable region contains at least part of the CDR sequences located as follows..." is maintained for reasons of record.

Applicant did not address this rejection in his response.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1, 2, 14, 17-20, 23, 29 and 32-43 under 35 U.S.C. 103(a) as being unpatentable over Spiers et al. (Canadian Journal of Microbiology, 1991, Vol. 37, pages 650-653) or O'Brien et al. (U.S. Patent 5,747,272) in view of Carter et al. (WO 94/04679) is maintained for reasons of record.

Applicant argues:

1. The rejection does not disclose what a standard sequence methodology is or how a worker would be motivated to use it to combine the cited references.

2. Dr. Wong states that the approach suggested by the examiner would not work and hence one of skill in the art would be dissuaded from isolating the sequence of the 13C4 and 11E10 murine antibodies.

3. Dr. Wong states that due to the genetic complexity of the 13C4 and 11E10 murine antibody variable regions would make using the Examiner's approach to isolate cDNA from a hybridoma library very difficult with no reasonable chance of success.

4. The approach taken by the inventors took into account the problems inherent to the approach proposed by the Examiner.

5. The PCR amplification problem (and its solution) is not disclosed by any of the cited references.

Applicant's arguments and the Declaration by Dr. Wong have been fully considered and deemed non-persuasive. As outlined previously, Spiers et al. and O'Brien disclose the 11E10 and 13C4 antibodies and Carter et al. disclose the methods of producing humanized antibodies. Furthermore, though the sequences of said antibodies where not explicitly disclosed it would have been standard practice for one of skill in the art to obtain said sequences utilizing standard sequencing methods. Moreover, it would have been equally obvious for one of skill in the art to employ the methodologies disclosed by Carter et al. to humanize the 13C4 and 11E110 antibodies in order to reduce the side effects associated with anti-mouse immunoglobulins since the process of humanizing a known antibody is well known in the art. It should be noted that Dr. Wong's arguments are predicated on the mistaken belief that the Examiner implied that the cloning approach described by Carter could be used to obtain the sequences of the 11E10 and 13C4 antibodies. As reiterated during the interview of 4-13-2004, said sequences could be obtained by standard protein sequencing methodologies. Dr Wong's arguments were directed to nucleotide sequencing not protein sequencing. Hence said arguments are not deemed persuasive. Finally, since the rejected claims are not product by process claims, the products disclosed by the cited references, in absence of evidence to the contrary, are deemed to be the same as those of the instant invention.

The rejection of claims 1, 2, 14, 17-20, 23, 29 and 32-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spiers et al. (Canadian Journal of Microbiology, 1991, Vol. 37, pages 650-653) or O'Brien et al. (U.S. Patent 5,747,272) in view of Shitara et al. (U.S. Patent 5,866,692) is maintained for reasons of record.

Applicant argues:

1. The rejection does not disclose what a standard sequence methodology is or how a worker would be motivated to use it to combine the cited references.

2. Dr. Wong states that the approach suggested by the examiner would not work and hence one of skill in the art would be dissuaded from isolating the sequence of the 13C4 and 11E10 murine antibodies.

3. Dr. Wong states that due to the genetic complexity of the 13C4 and 11E10 murine antibody variable regions would make using the Examiner's approach to isolate cDNA from a hybridoma library very difficult with no reasonable chance of success.

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Applicant's arguments and the Declaration by Dr. Wong have been fully considered and deemed non-persuasive. As outlined previously, Spiers et al. and O'Brien disclose the 11E10 and 13C4 antibodies and Carter et al. disclose the methods of producing humanized antibodies.

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Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Robert A. Zeman
May 13, 2004